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Endothelin-1 Antagonises Beta-Adrenergic Stimulation in Human Right Atrial Myocardium

S. J. Leslie¹, S. Prasad², C. Campanella², D. J. Webb¹, M. A. Denvir¹

Plasma concentrations of endothelin-1 (ET-1) are elevated in chronic heart failure (CHF) and correlate with a poor prognosis [1]. Short-term systemic ET blockade in CHF patients causes potentially beneficial haemodynamic effects; increasing cardiac output and reducing vascular resistance [2]. However, the initial results from longer term clinical trials have been disappointing. In the ENABLE and EARTH clinical trials preliminary reports indicate that there was no major benefit when an endothelin receptor antagonist (ETRA) was added to conventional heart failure therapy.

Beta-blockers improve mortality in CHF patients and while the mechanisms for these benefits are not fully understood they may involve beta₁-adrenoreceptor upregulation. Beta₁-adrenergic stimulation increases adenylate cyclase (AC), increasing cAMP, activating protein kinase A, resulting in phosphorylation of several intracellular proteins ultimately leading to an increase in intracellular calcium. The positive inotropic effect of ET-1 is mediated predominantly via the ET_A receptor resulting in activation of protein kinase C via G proteins. However, in isolated myocardial membrane studies ET-1 also inhibits AC and may therefore inhibit beta-adrenergic stimulation [3, 4]. This potentially important antagonism between the two systems has not been previously studied at a functional level.

Methods

12 right atrial appendage biopsies were harvested at the time of coronary artery bypass surgery and placed in cold cardioplegic solution ([mM]; NaCl 130, KCl 5.4, NaHPO₄ 0.56, MgCl₆H₂O 3.5, CaCl₂ 2, Glucose 10, HEPES 5, 2,3-butanedione-monoxime 30 [mM] corrected to pH 7.4 with NaOH). Free running trabeculae were mounted for electrical stimulation at 3 Hz at a voltage $\approx$ 10 % above threshold and allowed to stabilise for 1 hour in a vertical 7 ml chamber (World Precision Instruments, UK) containing modified Tyrodes (NaCl 130, KCl 5.4, NaHPO₄ 0.56, MgCl₆H₂O 3.5, CaCl₂ 2, Glucose 10, HEPES 5 [mM] corrected to pH 7.4 with NaOH and continuously bubbled with 100 % O₂ at 35 °C. ET-1 (Neosystem SNPE England, UK) was reconstituted in 0.9 % saline and isoprenaline (Sigma-Aldrich Chemicals, UK), a beta₁-adrenoreceptor agonist, was dissolved in physiological solution with ascorbic acid (1 mM) to reduce oxidation. Drug concentrations were chosen from previous dose ranging studies. Trabeculae were exposed to either isoprenaline (10 nM), ET-1 (10 nM) or isoprenaline followed by ET-1. When possible two trabeculae were dissected from a single atrial appendage.

Statistical difference was tested by Student's t-test (Excel 5.0, Microsoft). A value of $p < 0.05$ was considered to be statistically significant. All values are expressed as mean $\pm$ SEM.

The study was approved by the local research ethics committee and written informed consent obtained from each subject.

Results

ET-1 (10 nM) increased force by 12.6 ± 5.0 %, $n = 5$, $p = 0.04$. This was preceded by a transient non-significant decrease in force (-3.6 ± 1.9 %, $p = \text{ns}$). Isoprenaline (10 nM) increased force from baseline 65.7 ± 29.2 %, $n = 5$, $p = 0.01$. The increase in force with isoprenaline was of more rapid onset, with a maximal effect seen after 5 min (Fig. 1). When added to maximally beta-adrenergic stimulated trabeculae, ET-1 significantly attenuated the effect of isoprenaline causing a reduction in force (96 ± 39 %, $n = 5$, $p < 0.01$) (Fig. 2).

Discussion

Both ET-1 and isoprenaline increased isometric force in human RA myocardium. ET-1 increased force following a transient negative inotropic response, and although this has been described by other groups [4, 5] the mechanism remains unclear. Isoprenaline increased force, which was of faster onset and larger magnitude than ET-1. We have observed, for the first time, that ET-1 functionally attenuates the inotropic effects of isoprenaline in human myocardium. This reduction in force was observed after maximal stimulation of the beta-adrenergic system. The underlying mechanism is likely to be interaction at the level of AC as seen in isolated membrane studies where ET-1 was shown

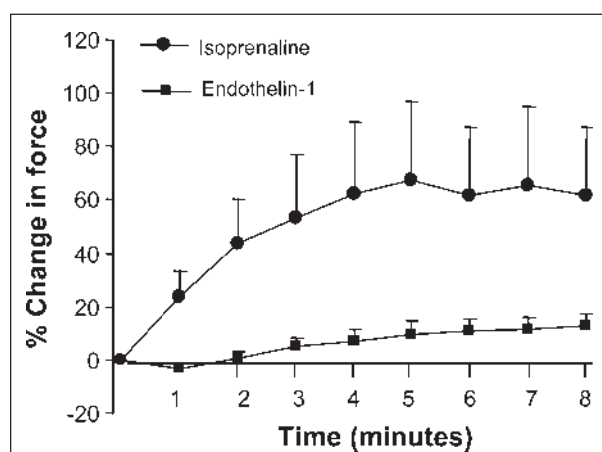


Figure 1. Effect of isoprenaline (10 nM) and endothelin-1 (10 nM) on force of contraction of human right atrial trabeculae

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to inhibit the effect of β_1 -adrenoreceptor activation on this enzyme.

This study has some limitations in that we were unable to study normal human ventricular myocardium due to a lack of suitable samples. Previous isolated membrane studies have confirmed differences between atrial and ventricular tissue so ET-1 may not inhibit AC in ventricular tissue [5]. In addition, the concentrations of ET-1 used were higher than those in the plasma of CHF patients but may be similar to those occurring at a local level in myocardium.

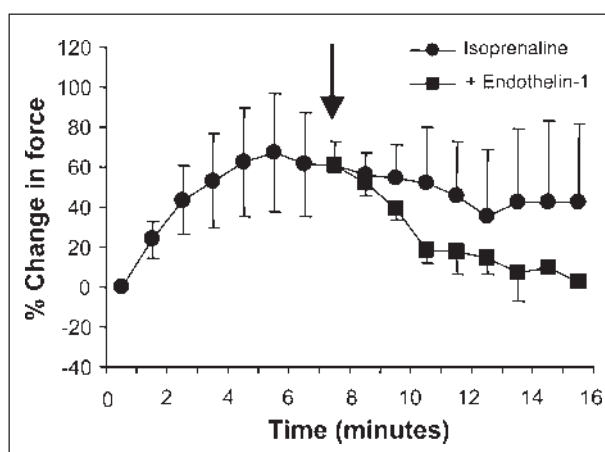


Figure 2. Effect of endothelin-1 (10 nM) on isoprenaline (10 nM) stimulated human right atrium; black arrow indicates the addition of endothelin-1 (10 nM)

The interaction between endothelin and adrenergic systems in the human myocardium may be significant in patients with CHF where both systems are activated. ET-1 may protect from catecholamines over-stimulation and may be anti-arrhythmic. With the possible introduction of ETARs for the treatment of CHF the physiological and patho-physiological interactions between these two systems may be of clinical importance as unintended deleterious effects may occur with ET blockade in the absence of β_1 -adrenoreceptor blockade.

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